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In re Application of	
Singer et al	
Application Number: 09/552,485	Filed: 4-18-00
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(54) NOVEL SYNTHESIS AND CRYSTALLIZATION OF PIPERAZINE RING-CONTAINING COMPOUNDS

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(57) **ABSTRACT**

The present invention is directed to methods for the preparation of piperazine ring-containing compounds, particularly mirtazapine. According to the present invention, the mirtazapine intermediate 1-(3-carboxypyridyl-2)-4-methyl-2-phenyl-piperazine is made by hydrolyzing 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine with a base where the base is present in a ratio of up to about 12 moles of the base per one mole of 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine. The mirtazapine intermediate 1-(3-carboxypyridyl-2)-4-methyl-2-phenyl-piperazine may be made by hydrolyzing 1-(3-cyanopyridyl-2)4-methyl-2-phenyl-piperazine with potassium hydroxide at a temperature of at least about 130° C. The method of the present invention also includes reacting 2-amino-3-hydroxymethyl pyridine with N-methyl-1-phenyl-2,2'-iminodiethyl chloride to form 1-(3-hydroxymethylpyridyl-2)-4-methyl-2-phenyl piperazine, and adding sulfuric acid to the 1-(3-hydroxymethylpyridyl-2)-phenyl-4-methylpiperazine to form mirtazapine. The present invention also relates to new processes for recrystallization of mirtazapine from crude mirtazapine.